REMARKS

I. Status of the Claims

Claims 1, 2, 35, 36, 39, 44, 50, 51, 59, 60, 66, and 67 are under consideration in this application and stand rejected. Claims 3-5, 42, 61-65, and 68-70 were withdrawn from consideration by the Examiner as being directed to non-elected subject matter and are herewith canceled without prejudice to or disclaimer of the subject matter recited therein.

By this Amendment, claims 1, 2, 44, 59, 60, and 66 are amended and claims 40, 41, and 55 are canceled. Claim 1 is amended to delete non-elected methods of treatment with compounds of formulas I-b, I-c, II-a, II-b, and II-c and the definitions of variables contained only within those formulas. The term "each" is deleted before the variables D, X^1, and Y in claim 1. Claim 1 is also amended to recite "provided that when the host has a *Orthomyxoviridae* or *Paramyxoviridae* viral infection, $R^{2'}$ and $R^{3'}$ are not simultaneously OH." Claim 2 is amended to recite "wherein the β-D nucleoside of formula I-a has variables X^1, Y^1, R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, and $R^{3'}$ selected from one of the following rows." Claim 44 is amended to depend only on claim 60. Claim 59 is amended to recite "wherein at least one of each R^4, $R^{4'}$, $R^{4''}$, R^5, $R^{5'}$ and $R^{5''}$." Claim 60 is amended to delete species where $R^{2'}$ and $R^{3'}$ are simultaneously OH and 3'-deoxycytidine. Claim 66 is amended to delete the phrase "or prophylaxis."

Applicant acknowledges the withdrawal of the prior rejections under 35 U.S.C. § 102(a) over Filippini et al., Archives of Virology, 145(5), 937-944, May 2000 and 35 U.S.C. § 102(e) over U.S. Patent No. 6,812,219 to LaColla et al.

II. Restriction Requirement

In the Office Action, Examiner required further restriction under 35 U.S.C. § 121 between the following groups of claims:

I. Claims 1 in part, 2, 35-36, 39-41, 44 in part, 50-51, 55, 59 in part, 60, 66, and 67, allegedly drawn to methods of treatment with compounds of formula I-a, classified in class 514, subclass 49.

II. Claims 1 in part, 3, 42, 44 in part, 59 in part, 61, and 68, allegedly drawn to methods of treatment with compounds of formula I-b, classified in class 514, subclass 45.

III. Claims 1 in part, 44 in part, 59 in part, 62 in part, and 63 in part, allegedly drawn to methods of treatment with compounds of formula I-c, classified in class 514, subclass 45.

IV. Claims 1 in part, 4, 44 in part, 59 in part, 64, and 69, allegedly drawn to methods of treatment with compounds of formula II-a, classified in class 514, subclass 49.

V. Claims 1 in part, 5, 44 in part, 59 in part, 65, and 70, allegedly drawn to methods of treatment with compounds of formula II-b, classified in class 514, subclass 45.

VI. Claims 1 in part, 44 in part, 59 in part, 62 in part, and 63 in part, allegedly drawn to methods of treatment with compounds of formula II-c, classified in class 514, subclass 45.

Office Action at 2-3. During a telephone conversation with the Examiner on August 29, 2008, Applicant provisionally elected without traverse the invention of Group I. Without acquiescing in the Examiner's characterizations and assertions regarding Applicant's claims and solely to expedite prosecution, Applicant affirms the election of Group I, claims 1 in part, 2, 35-36, 39-41, 44 in part, 50-51, 55, 59, 60, 66, and 67, without traverse. Applicant respectfully notes that claim 59 was elected in full since it depends on claims 1, 35, and 50, all of which are encompassed by Group I.

III. Claim Objection

The Examiner objects to claim 1 as containing non-elected subject matter. *Id.* at 6. Applicant amends claim 1 to delete non-elected methods of treatment with compounds of formulas I-b, I-c, II-a, II-b, and II-c, the subject matter of Groups II-VI, rendering this objection moot.

IV. Rejections Under 35 U.S.C. § 112

The Examiner rejects claim 66 under 35 U.S.C. § 112, first paragraph. According to the Examiner, the specification "while being enabling for treating the viral infections, does not reasonably provide enablement for prevention of the same." *Id.* at 6. Applicant respectfully disagrees with the Examiner. Solely in order to expedite prosecution, Applicant has amended claim 66 to delete "or prophylaxis." Applicant submits that this amendment renders the rejection for alleged non-enablement moot and respectfully requests that the rejection be withdrawn.

The Examiner rejects claim 2 under 35 U.S.C. § 112, second paragraph, as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." *Id.* at 9. The Examiner asserts that the table in claim 2 does not list all of the variables of a nucleoside of formula I-a and it is unclear what moiety is intended to be D. *Id.* Applicant respectfully disagrees with the Examiner. Solely in order to expedite prosecution, Applicant has amended claim 2 to recite "wherein the β-D nucleoside of formula I-a has variables X^1, Y^1, R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, and $R^{3'}$ selected from one of the following rows." In view of this amendment, Applicant respectfully requests withdrawal of the rejection.

V. Rejection Under 35 U.S.C. § 102

The Examiner rejects claims 1, 2, 41, 44, 60, and 67 under 35 U.S.C. § 102(a), as allegedly being anticipated by WO 98/18324 to Loeb et al. ("Loeb"). Office action at 9-10. The Examiner asserts that Loeb "disclose[s] methods of treating various viral infections, including HCV, flavivirus, influenza virus, measles, mumps, and RSV (see page 7, lines 23-35) with various modified nucleosides, such as N4-aminocytidine, 5-hydroxycytidine (page 26, 1st full paragraph) and 5-hydroxyuridine (page 9, line 21)." *Id.* at 10.

Applicant respectfully submits that the instant amendments render the rejection over Loeb moot. The nucleoside analogs described in Loeb and identified by the Examiner are naturally occurring ribonucleoside analogs with hydroxyl groups at the 2', 3', and 5' position of the ribose (i.e., in Applicant's formula I-a, D is hydrogen and $R^{3'}$ and $R^{2'}$ are OH). Claim 1, as currently amended, recites "provided that when the host has a *Orthomyxoviridae* or *Paramyxoviridae* viral infection, $R^{2'}$ and $R^{3'}$ are not simultaneously OH." Likewise, claim 60 is amended to delete species where $R^{2'}$ and $R^{3'}$ are simultaneously OH. Claims 40, 41, and 55 are canceled.

VI. Rejection Under 35 U.S.C. § 103

In the Office Action, the Examiner rejects claims 1, 2, 35, 36, 39-41, 44, 50-51, 55, 59-60, 66, and 67 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Loeb as applied to claims 1, 2, 41, 44, 60, and 67 and further in view of Filippini et al. (Arch Virol (2000), 937-944) ("Filippini"), U.S. Patent No. 6,812,219 to LaColla et al. ("LaColla"), and Shealy et al. (J. Med. Chem., 1986 (29) 1720-25) ("Shealy"). The Examiner asserts that Loeb "teaches [treating] various viral infections with modified

nucleosides which induce a mutation in the virus wherein the increase in mutation rate results in a reduced viability of progeny generations of the virus. Various modified nucleosides administered include 5-hydroxycytidine and N4-aminocytidine, which are encompassed by the claims as set forth supra." Office Action at 11. According to the Examiner, "Filippini teaches methods of treating HCV and HIV patients with various nucleosides such as zalcit[a]bine, which is a 2',3'-dideoxynucleoside;" LaColla discloses "a multitude of modified nucleosides, including 2',3'-dideoxy nucleosides, for the treatment of flavivirus and HCV infections;" and Shealy teaches "that various 5-halocytosine compounds have analogous properties in inhibiting viral replication." *Id.* at 11-12. In view of the above references, the Examiner asserts that "[i]t would have been obvious to one of ordinary skill in the art to modify the various nucleosides of the prior art to treat various viral infections with these references before them," based on the expectation "that compounds similar in structure will have similar properties." *Id.* at 12. Applicant respectfully disagrees and traverses for at least the following reasons.

Several basic factual inquires must be made in order to determine whether the claims of a patent application are obvious under 35 U.S.C. § 103. These factual inquiries, set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 U.S.P.Q. 459, 467 (1966), require the Examiner to:

> (1) Determine the scope and content of the prior art;
> (2) Ascertain the differences between the prior art and the claims in issue;
> (3) Resolve the level of ordinary skill in the pertinent art; and
> (4) Evaluate evidence of secondary considerations.

383 U.S. at 17, 148 U.S.P.Q. at 467. The obviousness or non-obviousness of the claimed invention is then evaluated in view of the results of these inquiries. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467; *see also KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1734 (2007). It is important to note that a prior art reference relied upon in a rejection "must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." M.P.E.P. § 2141.02(VI).

In the present case, the Examiner has not established a prima facie case of obviousness. In order to establish a prima facie case of obviousness, the Examiner first must show that the prior art references teach or suggest all the claim limitations. *See In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). Here, the Examiner has not met that burden because Loeb, Filippini, LaColla, and Shealy fail to teach or suggest all of Applicant's claim limitations. As discussed in Section V, claims 1, 2, 44, 60, and 67, as currently amended, do not recite naturally occurring ribonucleosides for the treatment of *Flaviviridae*, *Orthomyxoviridae*, or *Paramyxoviridae* viral infection. The Examiner admits that Loeb does not teach "the additional various claimed compounds for treating the viral diseases." Office Action at 11.

The key, moreover, "to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious." M.P.E.P. § 2141(III). The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Id.*, citing *In re Kahn*, 441 F.3d 977, 988, 78 U.S.P.Q.2d 1329, 1336 (Fed. Cir. 2006). Applicant respectfully submits that such articulated reasoning is not

present in the rejection of record at least because no rationale is set forth for why one of ordinary skill in the art would have modified the naturally occurring ribonucleosides described in Loeb.

In support of his rejection the Examiner relies on *In re Payne*, 606 F.2d 303, 203 U.S.P.Q. 244, 254-55 (C.C.P.A. 1979) to contend that "[w]here the prior art compounds essentially bracket the claimed compounds and are known to be effective as well known pesticides, for example, one of ordinary skill in the art would be motivated to make the claimed compounds in searching for new pesticides." Office Action at 12. The Examiner then asserts that "it would be obvious to treat other members of Flaviviridae, Orthomyxoviridae, or Paramyxoviridae viral infections with the same drugs, as Loeb teaches that overlapping modified nucleosides can be used to treat all of the above classes of viral infections." *Id.*

However, the Federal Circuit has explained that a prima facie case of obviousness regarding a claimed compound that is structurally similar to a prior art compound is only made out when the prior art gives reason or motivation to make the claimed compound. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007). The court also explained that "[i]n addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure." *Id.* The court noted that while a "known compound may suggest its homolog, analog, or isomer because such compounds 'often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties'", it still remains necessary in cases involving new chemical

compounds "to identify *some reason that would have led a chemist to modify a known compound in a particular manner to establish a prima facie case of obviousness of a new claimed compound.*" *Id.* (emphasis added). The Federal Circuit went on to confirm that the test outlined above for establishing a prima facie case of obviousness of a claimed compound that is structurally similar to a prior art compound is consistent with the legal principles set forth in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). *Id.*

Here, the Examiner has merely provided general statements asserting that "overlapping modified nucleosides" in Loeb are structurally similar without pointing to any additional facts demonstrating that it would have been obvious to one of ordinary skill in the art to use the currently claimed deoxynucleosides and dideoxynucleosides containing various substituents on both the nucleoside base and sugar in the treatment of *Flaviviridae, Orthomyxoviridae*, or *Paramyxoviridae* viral infection. *See* Office Action at 12.

Loeb is directed to the identification and use of naturally occurring ribonucleoside analogs to induce a mutation in a RNA virus in order to inhibit viral replication. Loeb reports, in general, libraries containing up to a million different undefined ribonucleoside analogs comprising a "random chemical substituent" covalently linked to various permutations of uridine, guanosine, cytidine, and adenosine. Loeb at 9. Loeb then provides methods for screening these libraries for antiviral activity that include incorporating a ribonucleoside analog into a viral RNA *via* a viral RNA polymerase. A determination is then made whether the incorporation causes a mutation in the virus. *Id.* at 8. In this regard, it is suggested that mutagenic RNA nucleoside analogs in

general may be administered to a patient suffering from any one of a lengthy laundry list of known viruses, among them dengue fever, yellow fever, and HCV. *Id.* at 33.

The compounds of Loeb must contain a ribose where the 2', 3', and 5' position of the ribose is substituted with -OH. *Id.* at 25; *see* Declaration of Michael J. Otto ("Declaration"), filed concurrently herewith, at ¶ 3. There is no disclosure of other substituents at these positions nor is there a disclosure of using deoxynucleosides or dideoxynucleosides. In fact, Loeb specifically teaches away from using nucleoside analogs other than naturally occurring ribonucleosides. "The methods of the invention do not use mutagenic deoxyribonucleotides that are incorporated into cellular DNA." Loeb at 21. Loeb also teaches that non-naturally occurring ribonucleoside analogs, the very compounds recited in the rejected claims, may act by a different mechanism that does not cause a mutation in the virus. *See* Declaration at ¶¶ 3-4. Loeb states that the preferred nucleoside analogs can be incorporated and extended by a polymerase. *Id.* at ¶ 3. "Thus, unlike certain viral inhibitors which cause chain termination (e.g., analogs lacking 3'-hydroxyl group), the preferred analogs of the present invention are non-chain terminating analogs that generally do not result in the termination of RNA synthesis upon their incorporation." Loeb at 22. Accordingly, Loeb's disclosure is clearly limited to the use of naturally occurring ribonucleosides that do not result in termination of RNA synthesis upon their incorporation.

In contrast to Loeb, Applicant's compounds work via a different mechanism. Applicant's claims encompass deoxyribose and dideoxyribose nucleosides for the treatment of *Flaviviridae*, *Orthomyxoviridae*, or *Paramyxoviridae* viral infection or abnormal cellular proliferation. In contrast to the compounds disclosed by Loeb, as

explained in the Declaration, the currently claimed nucleosides, once metabolized and incorporated, "cause the incorporation process to be terminated immediately following the newly incorporated nucleotide. No mutational event occurs during this type of inhibition." Declaration at ¶ 4. Moreover, it would not have been obvious from Loeb that deoxyribose and dideoxyribose nucleosides could also be used to treat *Flaviviridae*, *Orthomyxoviridae*, or *Paramyxoviridae* infection, since these viruses are RNA viruses that do not have a DNA phase as part of their life cycle. Declaration at ¶ 5. The claimed deoxyribose and dideoxyribose nucleosides are effective against RNA viruses. *See* Declaration ¶ 6.

The other references cited by the Examiner, Filippini, La Colla, and Shealy, do not provide the necessary teaching or suggestion to modify the naturally occurring ribonucleosides described in Loeb to produce the claimed deoxyribose and dideoxyribose nucleosides. The Examiner asserts that Applicant's proviso excluding zalcitabine at the end of claim 35, for example, "is not seen to render patentable the claim, as the compound delimited would still be seen as obvious to treat other flavivirus infections, for example, or treat the flu." Office Action at 12.

In Filippini, zalcitabine, a drug approved by the Food and Drug Administration to treat human immunodeficiency virus (HIV), was administered in combination with zidovudine, another antiretroviral nucleoside analog, and indinavir, an HIV-protease inhibitor, to a population of HIV and HCV co-infected patients and also to a second population infected with HIV only. Filippini at page 938. Filippini's purpose in conducting the study was to evaluate the impact of new antiretroviral combinations on HCV replication and liver enzyme levels in HIV and HCV co-infected patients. *Id.* While

Filippini may have inherently treated patients infected with HCV with zalcitabine while using that drug to treat HIV, it neither teaches or suggests using zalcitabine (2',3'-dideoxycytidine) or any other nucleoside to treat other flavivirus infections or the flu nor further modifying 2',3'-dideoxycytidine to treat HCV infection.

The Examiner asserts that "modifying zalcitabine with a 5-fluoro group on the base would also be obvious, as various 5-halogen cytidine compounds are taught to be effective in Loeb et al. (see cytidine compounds on page 26) and Shealy et al." Office Action at 12. As discussed above, Applicant respectfully submits that Loeb describes only naturally occurring ribonucleosides that act by a completely different mechanism than dideoxynucleosides, which are generally considered to cause termination of RNA synthesis upon their incorporation. *See* Declaration ¶ 6.

Shealy also fails to provide the necessary teaching or suggestion to modify zalcitabine with a 5-fluoro group. Shealy is directed to a completely different class of nucleosides than the presently claimed ribonucleoside analogs. Shealy describes carbocyclic analogues, where the sugar contains all carbon atoms instead of the heterocyclic ribose sugar. Moreover, while Shealy describes 5-chloro and 5-bromo derivatives of carbodine and C-2'-deoxycytidine and the 5-iodo derivatives of carbodine, C-2'-deoxycytidine, C-3'-deoxycytidine, and C-ara-C, it does not describe substituting a 5-fluoro group on any of the carbocyclic analogues. Because changes in either the structure of the sugar or base component of nucleoside compounds may have an unpredictable effect on biological activity, one of ordinary skill in the art would not have had the motivation to alter both the type of sugar and substituent at the 5-position of the

base to yield 5-fluoro-2',3'-dideoxycytidine recited in claim 36, for example. Nor would the skilled artisan have had an expectation of success in doing so.

Applicant also respectfully submits that LaColla does not disclose 2',3'-dideoxy nucleosides for the treatment of flavivirus and HCV infections, contrary to the Examiner's statement on page 11 of the Office Action. Column 143, line 18 of LaColla describes the species 3'-methyl, 2'-deoxycytidine, not 3'-methyl, 2',3'-dideoxycytidine. Columns 143 and 144 in LaColla describe 2'-deoxynucleosides substituted at the 3'-position with either methyl, trifluoromethyl, or 2-bromo-vinyl. None of Applicant's currently claimed species for the treatment of *Flaviviridae* or HCV viral infection contain a methyl, trifluoromethyl or 2-bromo-vinyl substituent on the sugar. Accordingly, since Filippini, Shealy, and LaColla do not provide the necessary teaching or suggestion to modify the naturally occurring ribonucleosides described in Loeb to produce the claimed deoxyribose and dideoxyribose nucleosides, Applicant respectfully requests the withdrawal of this rejection.

Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

If the Examiner believes a phone call would be useful in resolving outstanding issues, if any, he is respectfully invited to contact the undersigned at 202-408-4069.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: March 10, 2009

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Attachment: Declaration of Michael J. Otto, Ph.D.